Update on Medications for Diabetes, Cardiovascular Diseases and their Related Complications

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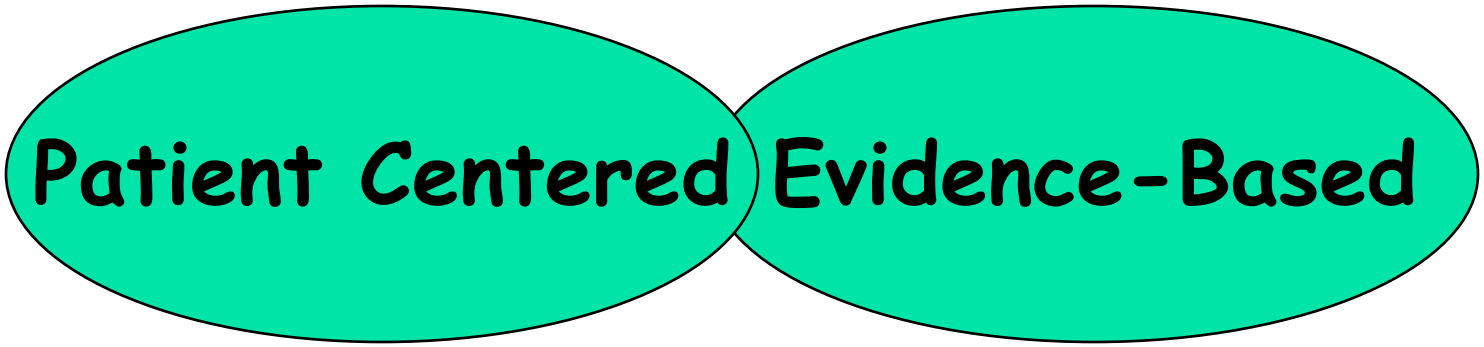
Topics for Discussion

- Patient safety/ medication adherence
- Key studies
- New FDA warnings
- New dosage forms/ new products
- Controversies in treatment of hypertension/dyslipidemia and use of antiplatelet/anticoagulant drugs

Safe and Effective Medication Prescribing



Evidence-based Resources for Information on New Medications

- Prescribers' Letter
  - www.prescribersletter.com
- Medical Letter and Treatment Guidelines
  - www.medicalletter.org

Improving Medication Adherence: Practical Considerations

- Consider cost of medication
  - Formulary inclusion and copay tier
  - Use generics if available
- Reduce pill burden and co-pays with rational combination products
  - Especially helpful with new Medicaid limits
- Consider ‘pill-splitters’ for flat priced drugs
  - Examples: Crestor®, Lipitor®

Thank Goodness for the‘$4 Walmart (Kroger,Target, Kmart ….) lists’

30 day, 90 day women’s health and OTC programs
$4 or $9 for 30 day supply, $10 for 90 daysupply

Walmart http://www.walmart.com/catalog/catalog.gsp?cat=546834
Target http://sites.target.com/site/en/health/generic_drugs.jsp

90 day only programs--Kmart is $15, Walgreens is $12

Kmart https://pharmacy.kmartcorp.com/index.jsp
Walgreens https://webapp.walgreens.com/MYWCARDWeb/pdf/Value-PricedGenericsList.pdf

Publix- 7 **FREE** antibiotics -I remember these as the “ABCCDEF” meds- kids suspensions, too! Amoxicillin (& PCN), Bactrim, Cephalexin and Cipro, Doxy (& tetracycline), Eryth, and Flagyl.

Don’t forget www.needymeds.com !

Anderson Reduced-Price Formularies & South Carolina Medicaid Formularies

The South Carolina Medicaid Managed Care plans accepted at the FMC all have different formularies. The links at right are the Feb 2009 sites. Prior Authorization form links have been added on 2-16-09)

SC Medicaid & Managed Care Formularies

Plain Medicaid (click here for Prior Authorization form for SC Medicaid)

First Choice /Select Health (PA form here)

Amerigroup (no PA form online; call Amerigroup Pharmacy at 800-454-3730 for PA)

Unison (Basic PA form here; Certain drug classes, like PPI's have their PA forms here)

Blue Choice Medicaid (PA form here)

Reduced Price Formularies

AnMed Health (started Jan 2, 2009)

WalMart (30 and 90-day programs)

Kmart (90-day program)

Locally, WalMart, Kmart, Target, Publix, Walgreens, Rite-Aid, and AnMed Pharmacies have reduced price formularies. For Feb 2009, the links are below. (Anderson, SC)

http://formularies.googlepages.com/home
Courtesy of Matt Cline, MD

Clinical Trials
Potential Practice Changers

- JUPITER
  - Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin
- ONTARGET
  - The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial
- ACCOMPLISH
  - Avoiding Cardiovascular Events in Combination Therapy in Patients Living with Systolic Hypertension
- POPADAD
  - Prevention of Progression of Arterial Disease and Diabetes

Topics for Discussion:

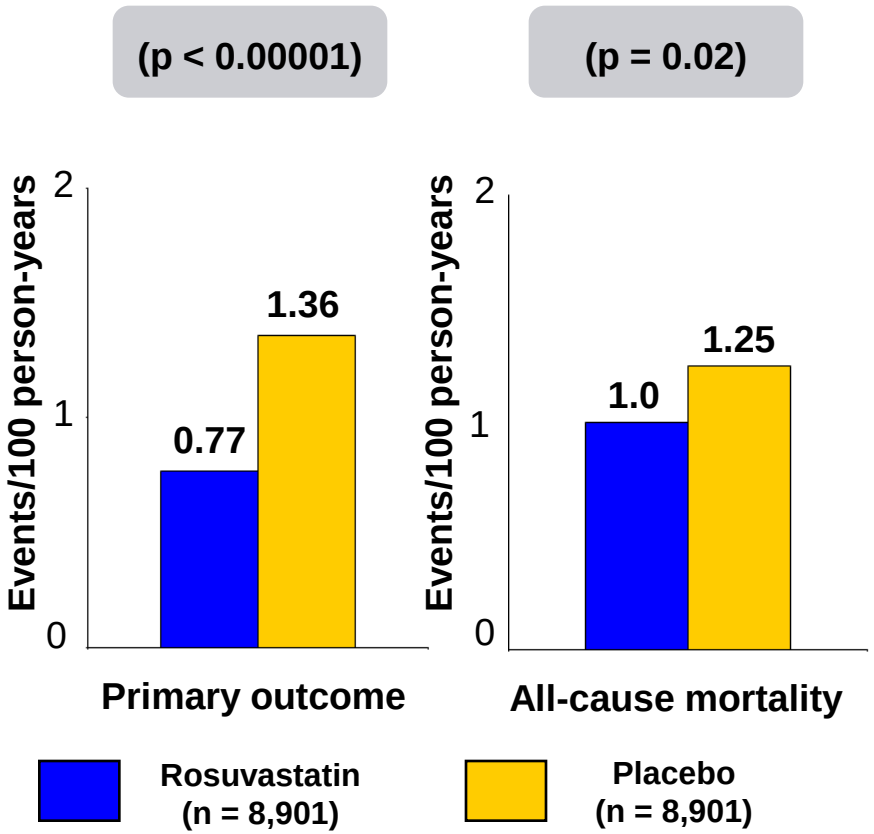
Dyslipidemia

- Statins for primary prevention of CVD
  - Should we put ‘Statins’ in the drinking water?
  - Impact of JUPITER trial
- Update on Vytorin® controversy
  - Effectiveness and cancer risk
- Update on role of fibrates in lipid therapy
  - Combination with statins
  - Trilipix® (delayed release fenofibric acid)

JUPITER

Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin

Trial design: Apparently healthy patients with LDL cholesterol <130 mg/dl and hs-CRP ≥2 mg/L were randomized to rosuvastatin 20 mg daily or placebo. Clinical outcomes were compared at a median of 1.9 years.



Results

- Rosuvastatin associated with a significant ↓ in the primary outcome of MI, stroke, unstable angina, revascularization, or cardiovascular death (HR 0.56, 95% CI 0.46-0.69, p < 0.00001)
- All-cause mortality ↓ with rosuvastatin (p = 0.02)
- Serious adverse effects were similar (p = 0.60)

Conclusions

- Rosuvastatin was associated with a significant reduction in major cardiovascular events, including death, in patients with LDL <130 mg/dl, but high hs-CRP (≥2.0 mg/L)
- May require revision of current guidelines

Ridker PM, et al. NEJM 2008;359:2195-207

Presented by Dr. Paul Ridker at AHA 2008

Dyslipidemia

Role of Fibrates

- Fibrates (gemfibrozil, fenofibrate, fenofibric acid) primarily ↑HDL and ↓triglycerides
- Concomitant use with statins recommended if non-HDL and triglycerides remain high
  - No evidence of improved CV morbidity or mortality compared to statin monotherapy
  - Associated with increased risk of myopathy and rhabdomyolysis
    - Noted most often with gemfibrozil; rare reports with fenofibrate

Dyslipidemia

Role of Fibrates

- Mutiple fenofibrate formulations and dosage strengths increase risk of medication errors
- New product Trilipix® (delayed release fenofibric acid)
  - Active metabolite of fenofibrate
  - Only fibrate approved for use with statins
    - No significant difference in safety and efficacy of combination tx compared with fenofibrate
  - Fixed dose combo product of Trilipix/Crestor®
    - NDA to be submitted 2009

Dyslipidemia

Update on ezetimibe/simvastatin (Vytorin®) Controversy

- FDA review of final data from ENHANCE trial
  - Vytorin® no more effective than simvastatin alone for reducing progression of atherosclerosis
    - Despite greater lowering of LDL (56% vs 39%) changes in carotid artery thickness (surrogate marker) not statistically significant
  - Lowering LDL-C still important in reducing risk of CVD
  - Patients should not stop taking Vytorin® or other drugs
- IMPROVE-IT evaluating Vytorin effect on CV events
  - Scheduled to be completed 2012

www.fda.gov 2009

Topics for Discussion:

Hypertension

- Choice of thiazide diuretics
  - HCTZ, chlorthalidone or indapamide
- Combination therapy:
  - When and what to use?
- ACEI/ARB combination therapy
  - Benefits and risks

Hypertension

Choice of Thiazide Diuretics

- Hydrochlorothiazide (HCTZ) most frequently used
  - Chlorthalidone and indapamide also available
  - Chlorthalidone twice as potent as HCTZ with longer duration of action (12.5mg=25mg HCTZ)
- Chlorthalidone has been shown to be at least as effective as an ACE inhibitor or calcium channel blocker in preventing CV events (ALLHAT)
  - More effective than an ACE inhibitor in lowering BP in Black patients

Hypertension

Optimal Combination therapy

- Consider if >20mmHg systolic and/or >10mmHg diastolic above treatment goal
- ACCOMPLISH trial results
  - indicate ACEI/CCB (benazepril/amlodipine) vs ACEI/diuretic (benazepril/HCTZ) may be more effective at reaching cardiovascular outcomes in high risk patients
    - High risk: hypertension plus CVD, CKD, PAD, LVH or diabetes
    - Results may have been different if diuretic had been chlorthalidone or indapamide

Hypertension

ACEI/ARB combination therapy

- Combination offers no additional benefit compared to monotherapy with ACE inhibitors in patients with CAD, PAD, CVD or Dm with end-organ damage (ONTARGET)
  - Increases risk of hypotension and syncope and renal impairment compared to monotherapy
- Benefit of ACEI/ARB combination confirmed for patients with CHF who can not tolerate beta blocker or in patients with kidney disease not related to diabetes

Antiplatelet Therapy

- Low dose aspirin and risk of GI bleeding
  - Is a PPI necessary?
- Aspirin for primary prevention in Diabetes
- clopidigrel (Plavix) safety issues
- Genetic differences in response to antiplatelet drugs

Antiplatelet Therapy

Low dose aspirin and Risk of GI bleeding

- Daily low dose aspirin doubles risk of GI bleeding
  - One additional serious GI ulcer or bleed for every 200 patients on low dose per year
- Enteric coated or buffered aspirin do not prevent GI ulcers or bleeding
- H2 blockers such as ranitidine do not prevent ulcers related to aspirin or NSAIDs
- Consider PPI for high risk patients
  - History of ulcers, chronic NSAIDs, corticosteriods, Plavix , warfarin, age>60

Antiplatelet Therapy

Aspirin for Primary Prevention in Diabetes

- Two new studies (POPADAD and JPAD) suggest that aspirin is not useful for primary prevention
- ADA guidelines support use of aspirin for patients over 40 or have other cardiac risk factors (smoking, BP, lipids, family history)
  - Level C evidence
- Strong evidence supports use of Aspirin for secondary prevention

Antiplatelet therapy

Clopidogrel (Plavix) safety issues

- Interactions with proton pump inhibitors (PPIs)
  - Inhibit enzyme CYP2C19 necessary to convert prodrug to active component
  - Most likely to occur with omeprazole (Prilosec®); least likely with pantoprazole (Protonix®)
- ‘Resistance’ due to genetic differences
- ? Increased risk of death and MI with abrupt withdrawal of therapy

Diabetes Mellitus

- Revised ADA Guidelines for Type 2 Diabetes initial therapy
  - Diabetes Care 2008;31(12):1-11
- New products and delivery devices
  - Januvia/Janumet®
  - Symlin®, FlexPen®, Kwik® pens
- New warnings
  - Byetta® -pancreatitis
  - TZDs – fracture risk

ADA Guidelines for Type 2 Diabetes (Revised)

- Initial therapy: lifestyle changes and metformin
- Tier 1 add-on: sulfonylureas or insulin
  - TZDs (pioglitazone and rosiglitazone) removed as option
- Tier 2 add-on options: GLP-1 analog exenatide (Byetta®) and pioglitazone (Actos®)
- Other therapeutic options (pramlintide, sitagliptan, meglitinides, acarbose) considered as less optimal options
  - Lack of outcomes data

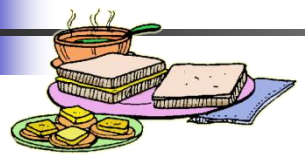
Diabetes Care 2008;31(12):1-11

Incretins

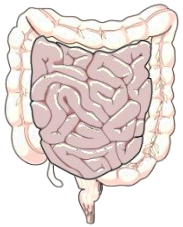
- Gut hormones that enhance insulin secretion in response to food *"glucose dependent"*
  - Glucose dependent insulinotropic polypeptide (GIP)
  - Glucagon–like peptide (GLP-1)
    - Secreted from L cells in small intestine
    - Diminished activity in Type 2 diabetes
- Incretin mimetics
  - Mimic glucoregulatory effects of GLP-1
- DPP-4 inhibitors
  - Extend half-life of endogenous GLP-1

Role of Incretins in Glucose Homeostasis

Ingestion of food



GI tract



Release of gut hormones — Incretins[1,2]

Active GLP-1 & GIP

Inactive GLP-1

Inactive GIP

DPP-4 enzyme

Pancreas[2,3]

Beta cells
Alpha cells

Glucose-dependent
↑ Insulin from beta cells (GLP-1 and GIP)

↑ Glucose uptake by muscles[2,4]

↓ Glucose production by liver

Glucose dependent
↓ Glucagon from alpha cells (GLP-1)

↓ Blood glucose

DPP-4 = dipeptidyl-peptidase 4

1. Kieffer TJ, Habener JF. *Endocr Rev*. 1999;20:876–913.
2. Ahrén B. *Curr Diab Rep*. 2003;2:365–372.
3. Drucker DJ. *Diabetes Care*. 2003;26:2929–2940.
4. Holst JJ. *Diabetes Metab Res Rev*. 2002;18:430–441.

DPP- 4 inhibitors

- DPP- 4 dipeptidyl peptidase
  - Enzyme that inactivates gut hormone, glucagon-like peptide (GLP-1) and GIP
  - If blocked, hepatic glucose production is reduced and glucose (meal) stimulated insulin secretion is increased
  - Minimal suppression of appetite; weight neutral
  - Does not slow gastric emptying
  - May restore beta cell mass and inhibit beta cell apoptosis

DPP-4 Inhibitors

Agent	Status	Comments
Sitagliptan (Januvia®) *Merck*	Available in US and Europe	25, 50,100mg tabs Also available in combo with metformin (Janumet®) 50/500, 50/1000 mg
Vildagliptan (Galvus) *Novartis*	Available in Europe; pending FDA approval	Original Approval denied; additional safety requested due to concerns over skin toxicity
Alogliptin -*Takeda/ PPD*	NDA submitted to FDA 2008	
Saxagliptan - *BMS*	Phase 3 trials	

DPP-4 Inhibitors Questions and Issues

- Place in therapy
  - Monotherapy versus combination therapy
  - Special populations: geriatrics
- Adverse effects
  - Potential effects on other DPP enzymes; hypersensitivity reactions
- Combination with GLP-1 analogs
  - Theoretical benefit; no clinical advantage
- Outcomes data
  - No morbidity and mortality trials in progress

Exenatide (Byetta®)

- Glucagon-like peptide-1 (GLP-1) agonist (incretin mimetic)
  - Derived from the saliva of the Gila monster
- Mechanism of action
  - Potentiates insulin secretion
    - Restores both 1rst and 2nd phase insulin release
  - Inhibits secretion of glucagon
    - during periods of hyperglycemia only
  - Slows gastric emptying
  - Promotes satiety and decreased food intake

GLP-1 analogs

Exenatide (Byetta) Questions and Issues

- Monotherapy indication
  - NDA filed; FDA approval ?2009?
- Combination/comparison with insulin
  - Endocrine practice 2007;13(5):444-450
  - Clinical therapeutics 2007 (online pub november 27)
- Special populations
  - Adolescents
- Comparison with liraglutide
  - No direct comparator trials available

GLP-1 analogs

Exenatide (Byetta) Questions and Issues

- Safety concerns/ risk of pancreatitis
- Comparison with sitagliptan
  - 2 week study demonstrated greater reduction in postprandial glucose with exenatide; similar reduction in fasting glucose
    - Curr Med Res Opin 2008(24):2943-2952
- Once weekly formulation (LAR)
  - Comparison with twice daily dosing

Exenatide (Byetta®)

Update on adverse effects- *FDA alert 8/18/2008*

- 6 postmarketing reports of hemorrhagic or necrotizing pancreatitis, which were associated with 2 deaths
  - Case 1: Hemorrhagic pancreatitis in morbidly obese who was over 400 pounds and who had extensive gallstone disease at autopsy
  - Case 2: complicated medical course that included necrotizing pancreatitis; patient had stopped BYETTA some months before hospitalization for pancreatitis occurred
- Risk noted in Precautions following 30 postmarketing reports of acute pancreatitis – FDA alert 10/2007

FDA alert 8/08

Exenatide (Byetta®)
Update on pancreatitis

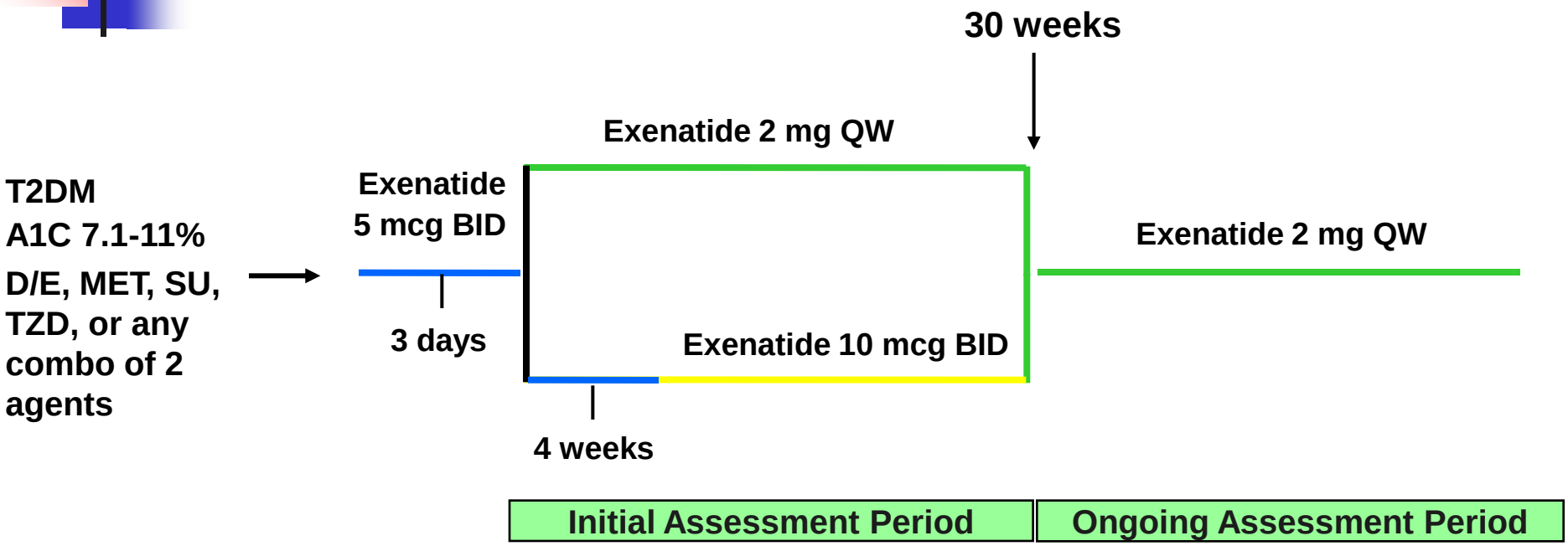
- Since launch of BYETTA in 2005, total of 6 deaths reported in patients who had experienced pancreatitis at some time
  - Four cases did not appear directly attributable to pancreatitis
- 10 cases of pancreatitis observed in clinical trials
  - Incidence rate of 1.81 (Byetta), 2.6 (placebo), 0.91 (insulin) per 1000 subject-years
- Spontaneous reporting rate for pancreatitis with BYETTA since launch
  - 0.34 events per 1000 patient years of exposure
    - 1 case per 3000 users for one year

Exenatide (Byetta®)
Update on pancreatitis

- Incidence of pancreatitis in general population
  - Rate of 0.33-0.44 per 1000 adults in US
    - 15-20% necrotizing; death occurs in 2-6% of cases
- Incidence of pancreatitis in Type 2 diabetes
  - Epidemiologic study found 3 fold greater incidence of acute pancreatitis compared with non-diabetic control population
    - 1.9 fold increase in biliary disease
      - Igenix (United HealthCare) database 2000-2005
- Risk factors for pancreatitis: gallstones, alcohol use, obesity, hypertriglyceridemia

DURATION-1

Diabetes Therapy Utilization : Researching Changes in A1C, Weight and Other Factors Through Intervention with Exenatide ONce Weekly)



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Published online Lancet Sept 8,2008

Data on file, Amylin Pharmaceuticals, Inc.
Drucker DJ, et al. Presented at ADA, 68th Scientific Sessions; 2008; San Francisco, CA

DURATION-1
Conclusions- Efficacy and Safety

- 77% of exenatide QW patients achieved A1C levels ≤7.0% at study endpoint
- Greater improvements in A1C (-1.9% vs -1.5%) and FPG (-42 mg/dL vs -25 mg/dL) than exenatide BID
- Similar weight loss over 30 weeks (~4 kg)
- Similar safety profile as exenatide BID
  - Reduced incidence of nausea with QW (26%) relative to BID (35%)
  - Nausea (26%) and injection site pruritus (18%) most common
- No major hypoglycemia, and no minor hypoglycemia in subjects not taking a concomitant sulfonylurea

Data on file, Amylin Pharmaceuticals, Inc.
Drucker DJ, et al. Presented at ADA, 68th Scientific Sessions; 2008; San Francisco, CA

GLP-1 analogs

Liraglutide *(NovoNordisk)* Questions and Issues

- Once daily synthetic GLP-1 analog
- FDA approval status
  - March 2, 2009 meeting to discuss NDA
- Clinical trials
  - **L**iraglutide **E**ffect and **A**ction in **D**iabetes (LEAD 1-5)
    - Liraglutide as monotherapy or add-on with amaryl, metformin, or metformin plus rosiglitazone
  - No published head-to-head trials with basal insulins or exenatide

LEAD 5
Conclusions

- Liraglutide given in conjunction with metformin and glimepiride:
  - Produces substantial improvements in mean glycemia (A1c) and reduces A1c significantly more than insulin glargine combined with the same two OADs (A1c liraglutide-based -1.33% vs. glargine-based -1.09%)
  - Achieves clinically relevant reductions in body weight, in contrast to an increase with insulin glargine (>3kg difference)
  - Is well tolerated, with modest and transient incidence of nausea

Russell-Jones D, ADA Scientific Sessions, Poster. June 8, 2008.

GLP-1 Receptor Agonists

	Exenatide (Byetta®)	Exenatide long-acting release (LAR)	Liraglutide
FDA approved	Yes	No	No
Route of administration	Sub-Q	Sub-Q	Sub-Q
Frequency of administration	Twice daily	Once weekly	Once daily
Half-life	2-4 hours	>1 week	12-14 hours
Dose per injection	5-10 mcg	Up to 2 mg	Up to 2 mg
Susceptibility to DPP-4 breakdown	No	No	No

Amylin Analogs:
Pramlintide acetate

- Mimics actions of beta-cell hormone, amylin
  - Amylin is co-located and co-secreted with insulin in response to food intake
  - Insulin plus **Amylin** deficiency occurs in both Type 1 and Type 2 diabetes
- Pharmacologic action
  - Slows gastric emptying
  - Suppresses inappropriately high postprandial glucagon secretion → reduced hepatic glucose production
  - Promotes satiety and reduction of appetite

Amylin Analogs

Pramlintide acetate (Symlin) What's new and on the Horizon

- New Dosing pen for Type 1 and Type 2 DM
- Once or twice daily dosing
  - Consider initiation with one dose at largest meal of the day to minimize risk of hypoglycemia and number of daily injections
- Use with basal insulin
  - Riddle M. Diabetes Care 2007: 2794-2799
- Use for weight loss

Symlin Pen

- New Dosing pen
  - Less potential medication errors
- Once or twice daily dosing
  - Consider initiation with one dose at largest meal of the day to minimize risk of hypoglycemia and number of daily injections